REMARKS

Claims 1-86 were previously cancelled. Claim 88 is presently cancelled. Accordingly, Claims 87 and 89-100 are currently pending. Accompnaying this Amendment is a 37 § 1.132 Declaration by Dr. Voorberg. This Declaration is not executed. An executed Declartion will follow shortly.

Paragraph 4 of the Office Action

In paragraph 4 of the Office Action, Claims 94 and 95 are rejected under 35 U.S.C. §112, second paragraph, as being indefinite. In particular, the Examiner states that:

> The recitation "binds the heavy chain of factor VIII" in claim 94 and the recitaion "binds the heavy chain of factor VIII consisting of the A1 domain, the A2 domain and the B domain of factor VIII" in claim 95, are ambiguous, claims 94 and 95 depend from claim 87, which recites VH sequences that only bind to the light chain of factor VIII. It is unclear how those sequences would bind to the heavy chain of factor VIII.

The Examiner misinterprets Claim 87. Claim 87 is a generic claim which encompasses (i) peptides binding to the **light chain** of factor VIII **and** (ii) peptides binding to the **heavy chain** of factor VIII.

Dependent Claims 94 and 95 are specifically directed to peptides binding to the heavy chain of factor VIII. For example, the peptides comprising SEQ. ID. NO: 51 or 53 are specific for the A2 domain of the factor VIII heavy chain. See Figure 11A.

Dependent Claims 96 and 97 are specifically directed to peptides binding to the light chain of factor VIII.

Apparently, the Examiner overlooked that Claim 87 encompasses both peptides binding to the light chain of factor VIII and peptides binding to the heavy chain of factor VIII. Applicants respectfully request withdrawal of this rejection.

Paragraphs 6, 7, 9 and 11 of the Office Action

In paragraph 6 of the Office Action, Claims 87, 88 and 91-99 are rejected under 35 U.S.C. §112, first paragraph, as containing new matter. In paragraph 7 of the Office Action, Claims 87, 88 and 91-100 are rejected under 35 U.S.C. §112, first paragraph, as not being enabled. In paragraph 9 of the Office Action, Claims 87, 88 and 92-99 are rejected under 35 U.S.C. §102(b) as being anticipated by WO 95/08336. In paragraph 11 of the Office Action, Claims 87 and 91 are rejected under 35 U.S.C. §103(a) as being unpatentably obvious over WO 95/08336 in view of Bird et al. (1998).

The Examiner states that Claims 89 and 90 "would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims." (Office Action page 7, paragraph 13.)

Claims 89 and 90 recite SEQ. ID. Nos. 23, 25, 27, 28, 32, 34, 36, 38, 51 and 53. Accordingly, Applicants have amended Claim 87 to recite only those sequences which are recited in Claims 89 and 90. Thus, Claims 87, 89 and 90 are allowable. Claims which depend on these allowable claims are also allowable.

In paragraph 7, the Examiner made an additional enablement rejection of indpendent Claims 98-100. These claims recite pharmaceutical compositions. The Examiner alleges that "it has been established that in the absence of a correlation between the *in vitro* and *in vivo* efficacy the person having ordinary skill in the art has no basis for perceiving these efficacy." (Office Action, page 4, 3rd full paragraph.)

Applicants respectfully assert that the Examiner has not stated the proper standard regarding the correlation of *in vitro* and *in vivo* examples and the claimed efficacy. In §2164.02 III of the M.P.E.P., it is stated:

> **CORRELATION: *IN VITRO/IN VIVO***
>
> The issue of "correlation" is related to the issue of the presence or absence of working examples. "Correlation" as used herein refers to the relationship between *in vitro* or *in vivo* animal model assays and a disclosed or a claimed method of use. An *in vitro* or *in vivo* animal model example in the specification, in effect, constitutes a "working example" if that example "correlates" with a disclosed or claimed method invention. If there is no correlation, then the examples do not constitute "working examples." In this regard, the issue of "correlation" is also dependent on the state of the prior art. In other words, if the art is such that a particular model is recognized as correlating to a specific condition, then it should be accepted as correlating unless the examiner has evidence that the model does not correlate. Even with such evidence, the examiner must weigh the evidence for and against correlation and decide whether one skilled in the art would accept the model as reasonably correlating to the condition. *In re Brana*, 51 F.3d 1560, 1566, 34 USPQ2d 1436, 1441 (Fed. Cir. 1995) (reversing the PTO decision based on finding that *in vitro* data did not support *in vivo* applications).
>
> Since the initial burden is on the examiner to give reasons for the lack of enablement, **the examiner must also give reasons for a conclusion of lack of correlation for an *in vitro* or *in vivo* animal model example**. A rigorous or an invariable exact correlation is **not** required, as stated in *Cross v. Iizuka*, 753 F.2d 1040, 1050, 224 USPQ 739, 747 (Fed. Cir. 1985). (Emphasis added.)

Applicants respectfully assert that the Examiner has **not** met the initial burden of giving reasons for a conclusion of lack of correlation. Thus, Applicants respectfully assert that this rejection is improper.

Moreover, there is a clear correlation between the working examples in the specification and the claimed invention. Claims 98-100 recite a pharmaceutical composition for the treatment of factor VIII inhibition. The pharmaceutical composition includes recombinant antibody fragments (termed scFv's) which bind specifically to factor VIII and interfere with the binding of inhibitory antibodies to factor VIII. The

recombinant antibody fragments of the invention bind specifically to the A2, A3-C1 and C2-domains of factor VIII.

The efficacy of these pharmaceutical compositions is demonstrated in the Examples by use of the Bethesda assay. The Bethesda assay is based on the ability of a patient's plasma containing the factor VIII inhibitor to inactivate factor VIII present in normal pooled plasma.

Using the Bethesda *in vitro* assay, Example 7 (beginning on page 29 of the specification) demonstrates that the recombinant antibody fragments of the present invention neutralize the activity of the factor VIII inhibitory murine monoclonal antibody. Example 10 (beginning on page 35 of the specification) demonstrates that the recombinant antibody fragments of the present invention neutralize factor VIII antibodies present in plasma of haemophilia A patients in the Bethesda *in vitro* assay.

The Bethesda assay is the most commonly used assay for diagnostic and therapeutic purposes to demonstrate the presence of an inhibitor to factor VIII.

As evidence, please refer to paragraph 2 of the accompanying 1.132 Declaration. There, Dr. Voorberg states "The Bethesda assay is recommended by the International Society on Thrombosis Haemostasis as a test for determining factor VIII inhibitors in plasma from patients. The Bethesda assay is used worldwide for the identification of factor VIII inhibitors."

To illustrate, Dr. Voorberg furnishes an article by Alan Giles *et al.* (*Thromb. Haemost.* 1998; 79: 872-5) written by members of the Scientific and Standardization Committee of the International Society on Thrombosis and Haemostasis. (See paragraph 4 of Dr. Voorberg's Declaration.) In the article, the Bethesda assay is characterized as follows:

> Subsequently, the Bethesda assay has achieved **international recognition** and is now the **most frequently used approach** for this purpose around the world. (See page 872, 2nd col., line 19.) (Emphasis added.)

Section 2164.02 III of the M.P.E.P specifically instructs that "if the art is such that a particular model is recognized as correlating to a specific condition, then it should be accepted as correlating..." Since the International Society on Thrombosis Haemostasis recommends the Bethesda assay as a test for assessing factor VIII inhibition, Applicants respectfully assert that the Examiner should accept the Bethesda assay as correlating to the claimed invention.

Accordingly, the data provided in the specification is sufficient to establish enablement. Thus, Applicants respectfully request withdrawal of the enablement rejection.

For the above reasons, allowance of the pending claims is earnestly requested. If the Exmainer has any questions regarding this amendment, he is invited to contact the undersigned at the telephone number listed below.

Respectfully submitted,

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